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10/618,088	07/14/2003	Elizabeth Jaffee	001107.00363	4098

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EXAMINER

BRISTOL, LYNN ANNE

ART UNIT	PAPER NUMBER
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1643

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/618,088	Applicant(s) JAFEE ET AL.	
	Examiner Lynn Bristol	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 September 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-112 is/are pending in the application.
- 4a) Of the above claim(s) 1-21, 25, 39-110 and 112 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 22-24, 26-38 and 111 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/28/06; 5/18/04; 9/11/03</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-112 are all the pending claims for this application.

Election/Restrictions

2. Applicant's election of Group 5 (Claims 22-38 and 111) and species to pancreatic cancer, the epitope of SEQ ID NO:2; and *Listeria monocytogenes* in the reply filed on September 11, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
3. Claims 1-21, 25, 39-110 and 112 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected groups 1-4 and 6-35 and nonelected species, there being no allowable generic or linking claim.
4. Claims 22-24, 26-38 and 111 are all the pending claims under examination with species to pancreatic cancer, the epitope of SEQ ID NO:2; and *Listeria monocytogenes*. The Examiner has withdrawn the species election for the epitope and the epitope species for SEQ ID NOS: 1 and 3-6 have also been examined on the merits.

Information Disclosure Statement

5. The U.S. patent and international application literature and the non-patent literature references cited in the IDS' of September 11, 2003, May 18, 2004 and April 28, 2006 have been considered and entered.

Specification

6. The specification on p. 32 is objected to because it does not provide a sequence identifier for the following sequence pursuant to 37 CFR 1.821 (c) and/or (d):

QVPLRPMTYK (SEQ ID NO:8).

Applicants are required to identify the sequence with the sequence identifier in addition to any other sequences that may not be properly identified.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 22-24, 26-38 and 111 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims,

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the quantity of experimentation which would be required in order to practice the invention as claimed.

Claims 22-24, 26-38 and 111 are drawn to a method for inducing a mesothelin-specific T cell response in a patient with a tumor overexpressing mesothelin comprising administering a vaccine comprising a polynucleotide encoding a polypeptide comprising an MHC Class I-binding epitope of mesothelin, where the tumor is a pancreatic tumor, the epitope is one or more of SEQ ID NOS:1-6, the polypeptide is mesothelin, mature mesothelin or a primary translation product, the vaccine comprises one or more polynucleotides, polypeptides bind to a plurality of allelic forms of MHC Class I molecules, polypeptides bind to a single allelic form of MHC, the polypeptide is selected using one or two algorithms, the T-cell response is induction of specific CD8+ T cells, the vaccine is acellular, the vaccine comprises *Listeria monocytogenes*, the vaccine induces tumor regression, and the vaccine keeps the patient tumor-free after removal of the tumor.

A) Disclosure of the specification and prior art is not enabling for inducing MHC Class I-restricted, mesothelin epitope-specific T cells with a mesothelin-epitope based vaccine in vivo

Claims 22-24, 26-38 and 111 are directed to inducing a T cell response in a patient by administering a polynucleotide encoding an MHC Class-I binding epitope of mesothelin.

1) Disclosure of the specification

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The specification teaches identifying and making MHC Class I restricted, CTL-specific peptides for mesothelin (SEQ ID NOS:1-6) based on computer algorithms. The specification teaches the in vitro measurement of mesothelin-specific T cell responses screened by antigen (peptides of SEQ ID NOS: 1 and 2)-pulsed T2 cells with CD8+ T cell enriched PBL from patients that have received an allogeneic GM-CSF secreting pancreatic tumor vaccine (Jaffee et al., J. Clin. Oncol. 19(1):145-156 (2001); cited in the IDS of 5/18/04). A summary of the ELISPOT results analyzing all 14 patients treated with the allogeneic vaccine on this study for the induction of mesothelin-specific CD8+ T cells following the first vaccination are shown in FIG. 2D. Each of the three DTH responders demonstrated a post-vaccination induction in T cell response to every mesothelin peptide that matched their respective HLA type. These data demonstrate that there is a direct correlation between observed post-vaccination in vivo DTH responses to autologous tumor, long term disease-free survival, and post-vaccination induction of mesothelin-specific T cell responses (Example 2; FIG 2D).

The specification teaches that "a mesothelin-specific T cell response represents a new candidate in vitro immune marker for predicting which patients will respond to this vaccine therapy" [0102]. While Applicants data may show that the mesothelin peptides are useful for predictive in vitro screening assays, the specification does not demonstrate a mesothelin epitope-specific T cell response generated in any animal model under conditions where the polynucleotide vaccine much less the polypeptide itself is administered to the animal.

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Applicants have not provided any evidence showing dosaging, route of administration, formulation, etc., in any animal tumor model that would allow one to even predict and extrapolate an effective dosage or amount of the inventive polynucleotide vaccine to induce a specific T cell response in an animal or a patient. Applicants are invited to supplement the record with evidence showing a correlative effect for the inventive vaccines producing mesothelin epitope-specific CTL induction in an animal model.

2) Disclosure in the prior art.

a) Mesothelin epitope peptides for inducing CTLs have been identified by other workers more recently (Yokokawa et al. Clin. Can Res. 11(17):6342-6351 (2005). Yokokawa discloses a mesothelin CTL epitope. T cell lines generated from a pancreatic cancer patient with the peptide showed high levels of lysis of mesothelin-expressing tumor cells and enhanced IFN-gamma and lymphotoxin production when target cells were pulsed with the peptide. Steinaa et al. (WO 00/20027; published 4/13/2000; filed 10/5/1999) discloses a method for inducing an immune response in an animal against a polypeptide antigen comprising administering vaccines comprising a polynucleotide encoding at least one CTL epitope derived from the polypeptide antigen such as mesothelin and a foreign T_H cell epitope and further comprising live vaccines including transfected bacterial strains (p. 46-55, 61). The results of searching relevant sequence databases using SEQ ID NOS:1-6 indicate that these amino acid sequences all map to portions of the amino acid sequence of mesothelin. Thus one skilled in the art would readily envisage that the mesothelin epitopes of SEQ ID NOS:1-6 would be inherent to

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the mesothelin polypeptide and CTL epitopes disclosed in the vaccine of Steinaa.

Steinaa teaches treating tumors but does not demonstrate a working example of the mesothelin polynucleotide vaccine on any tumor cell lines or an animal tumor model that would allow one skilled in the art to extrapolate the vaccine strategy to a patient.

Thus these prior art studies are hampered by the limitation that CTL induction was not examined in vivo for a peptide alone or a polynucleotide based vaccine much less for the expressed peptides encoded by the vaccine.

b) In general, the art of synthesizing functional equivalents of naturally occurring proteins is very unpredictable in nature. Although Schirle et al. (J. Immunol. Methods. 2001; 257: 1-16), for example, teaches that several computer algorithms are now available for use in predicting the structures of synthetic peptides that bind MHC molecules, Schirle et al. teaches, "the identified epitopes still have to pass the ultimate test: they have to prove to be useful in the in vivo situation" (page 11, paragraph bridging columns 1 and 2).

Moreover, Anderson et al. (Tissue Antigens. 2000 Jun; 55 (6): 519-531) teaches there is poor correspondence between predicted and experimental binding of peptides to class I MHC molecules; see entire document (e.g., the abstract). Andersen et al. teaches, while knowledge of the peptide binding motifs of individual class I MHC molecules permits the selection of potential peptide antigens, there is no strong correlation between actual and predicted binding when using predictive computer algorithms, and therefore the peptide binding assay remains an important step in the

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identification of cytotoxic T lymphocyte (CTL) epitopes, which cannot be substituted by predictive algorithms (abstract).

Furthermore, Feltkamp et al. (Mol. Immunol. 1994 Dec; **31** (18): 1391-1401) teaches, while efficient binding of peptide epitopes to MHC class I molecules is required to elicit an immune response against the peptide epitope or the intact antigen, an increased binding affinity does not consistently and reproducibly relate to a peptide epitope's immunogenicity, i.e., its ability to elicit a peptide- and antigen-specific immune response; see entire document (e.g., the abstract). Feltkamp et al. teaches that other factors, in addition to its binding affinity for an MHC molecule, determine whether a peptide epitope, or analogue thereof, will be able to stimulate an effective immune response; see, e.g., the abstract.

With respect to the general state of the art for peptide vaccine induction of CTLs, Beier et al. (USPN 2004/0037840; published 2/26/2004; filed 10/26/2001) discloses:

"It has been clearly demonstrated by several groups that tumour specific cytotoxic T cells (CTL's) are present in many tumours. These CTL's are termed tumour infiltrating lymphocytes (TIL's). However, these cells are somehow rendered non-responsive or anergic by several different possible mechanisms including secretion of immunosuppressive cytokines by the tumour cells, lack of co-stimulatory signals, down regulation of MHC class I molecules etc. There has been many attempts to isolate the tumour specific HLA class I bound peptides recognised by TILs, and in some cases it has also been successful (e.g. peptides from the melanoma associated antigens). Such peptides have been used to induce a tumour specific immune response in the host, but the practical use of tumour specific peptides in vaccines is restricted to a limited segment of the population due to the narrow HLA class I binding specificity of the peptides. Furthermore, it is usually relatively difficult to evoke a CTL response in vivo using synthetic peptides due to the low biological half-life of these substances as well as the difficulties with exogenous priming of MHC class I molecules." [0023-0024]

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c) Undue experimentation is required to practice the method. One cannot extrapolate the teaching of the specification to the claimed invention because the specification provides no exemplification of or guidance on how to use the claimed vaccine formulation or antigen for active immunotherapy in humans. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, ¶6).

The Examiner appreciates that "some experimentation does not necessarily equate to undue experimentation", but to advance the in vitro experiments disclosed in Example 2 of the specification into preclinical animal testing for entry into phase one clinical trials in human patients would not involve routine experimentation (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400,

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1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Neither the specification nor prior art are enabling for a method for inducing MHC Class I-restricted, mesothelin epitope-specific T cells when the vaccine is a polynucleotide which is further required to express one or more mesothelin epitopes in a patient subject in order to accomplish this endpoint.

B) Poor prognosis for pancreatic cancer challenges the predictability of anti-cancer therapeutics

Claims 22-24, 26-38 and 111 are directed to inducing a T cell response in a pancreatic cancer patient by administering a polynucleotide encoding an MHC Class-I binding epitope of mesothelin.

One of ordinary skill in the art at the time the instant application was filed, would have known that the prognosis for treating pancreatic cancer in any subject was extremely poor. Importantly, the prognosis for pancreatic cancer has not improved since, as according to Li et al. (Lancet 363:1049-1057 (2004)):

"Pancreatic cancer remains a major unsolved health problem, with conventional cancer treatments having little impact on disease course. Almost all patients who have pancreatic cancer develop metastases and die. The main risk factors are smoking, age, and some genetic disorders, although primary causes are poorly understood. Advances in molecular biology have, however, greatly improved understanding of the pathogenesis of pancreatic cancer. Many patients have mutations of the K-ras oncogene, and various tumour-suppressor genes are inactivated (Table 1). Growth factors also play an important part (p. 1051, Col. 1, ¶3-4). However, disease prognosis is very poor. Around 15-20% of patients have respectable disease, but only around 20% of these survive to 5 years. For locally advanced, unresectable and metastatic disease, treatment is palliative." (Abstract).

The research efforts to advance mesothelin as an immunotherapy in treating pancreatic cancer, ovarian cancer, mesothelioma and squamous cell carcinoma has been considered by others (see review by Hassan et al. Clin. Can. Res. 10:3937-3942 (2004)), but none have demonstrated the successful in vivo use of a mesothelin vaccine in a patient much less one encoded by a polynucleotide.

Thus, if Applicants are proposing that the inventive method to induce pancreatic cancer specific CTLs can be accomplished with a polynucleotide vaccine, then they have not shown with sufficient specificity that a) the vaccine could be targeted in vivo for uptake by APCs or dendritic cells, b) that the polypeptide is expressed at sufficient CTL-inducing levels from the polynucleotide, c) that mesothelin epitope-specific CTLs are cytotoxic for pancreatic cancer cell lines much less that for animal model correlates of pancreatic cancer(s), d) any CTL-inducing potential in a tumor patient for the claimed vaccine much less the mesothelin epitope peptides or e) the pancreatic tumor-preventative effect of the vaccine in any animal model.

C) Predictability of polynucleotide vaccine therapy in animal models versus human trials

Claims 22-24, 26-38 and 111 are directed to a polynucleotide vaccine encoding polypeptides for mesothelin epitopes.

The polynucleotide-based vaccine approach to eliciting antigen-specific immune responses has been rapidly developed since the early 1990s. Haupt (Exp Biol Med 227(4):227-237 (2002); Abstract cited in the IDS of September 11, 2003; full copy of

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reference attached hereto) teaches that DNA immunization has been demonstrated to provide tumor immunity and to elicit immune responses specific against a wide variety of tumor-associated antigens in animal models (see Table II), treatment of diverse hematological malignancies, B cell lymphomas, and human T cell leukemia virus type I (p. 232, Col. 2, ¶2). Haupt also teaches that difficulties with anti-tumor therapies involving DNA vaccination is in overcoming immunological tolerance to self antigens (p. 231, Col 1, ¶2 – Col. 2, Col. ¶1) as well as targeting different subpopulations of tumor cells that may express various tumor-associated antigens and different amounts of them. (p. 231, Col. 2, ¶2- p. 232, Col. 2, ¶2). With respect to extending DNA vaccines into humans, Haupt teaches that:

“Accumulating evidence suggests the usefulness of DNA vaccination for treating various tumors in animal models, but results from clinical trials are lacking and the therapeutic benefit in the prevention or treatment of malignancies in human beings remains to be proven.” (p. 233, Col. 2, ¶1),

and

“DNA vaccination is a promising strategy capable of inducing immune-mediated tumor reductions in animal model, but further studies are required to investigate the potential of DNA vaccination in antitumor treatment in human beings.” (p. 234, Col. 1, ¶1)

The specification does not teach any animal models showing the elicitation of antigen or epitope specific T cells for a pancreatic tumor expressing mesothelin antigen. It is known that the route of application of plasmid DNA as well as immunization schedule can determine the quality of the immune response generated. Haupt teaches that attempts have been made to increase the immune response following DNA

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immunization by varying the vaccination regime- combining different routes of vaccination or co-delivery of adjuvants (P. 230, Col. 2 to p. 231, Col. 1)

Thus, while the specification and the art references in this field disclose polynucleotide vaccines for use in inducing specific immune responses in animal models, one of skill in the art would be required to perform an unduly burdensome amount of experimentation to establish that vaccination with a polynucleotide encoding a mesothelin epitope could be readily transferred from animals to human patients.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required and the predictability of the art, in accordance with In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988), the preponderance of factual evidence of record indicates the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation to determine if each of the polynucleotide vaccine encoding any one or a combination of mesothelin epitopes of SEQ ID NOS:1-6 in which the claimed method is able to stimulate an effective T cell immune response against the native epitope of SEQ ID NOS: 1-6 or the native, intact mesothelin tumor antigen.

Conclusion

8. No claims are allowed.

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9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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